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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/757,298	01/14/2004	Robert S. Andrews	ISIS0038-100/CHEM0001US	5625

34138 7590 09/23/2005

COZEN O'CONNOR, P.C.
1900 MARKET STREET
PHILADELPHIA, PA 19103-3508

EXAMINER	
VIVLEMORE, TRACY ANN	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 09/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/757,298	ANDREWS ET AL.	
	Examiner	Art Unit	
	Tracy Vivlemore	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-40* is/are pending in the application.

4a) Of the above claim(s) *6,7,20-37,39 and 40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,8-19 and 38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of group I, claims 1-5, 8-12 and 38 in the reply filed on July 8, 2005 is acknowledged. The traversal is on the ground(s) that the reasons for asserting the unrelatedness of inventions I-XIII are not sufficient. These arguments are found persuasive with regard to these inventions and applicant's election of group I, with SATE as a phosphorus protecting group has been treated as an election of species. Thus, claims 1-5 and 8-19 and 38 will be examined with claims 1 and 13 designated as generic claims. The propriety of the restriction with regard to the relatedness of groups XIV-XVI has not been traversed.

Applicant additionally traverses the restriction requirement by asserting that a serious search burden has not been shown and points to the grouping of each of inventions I-XIII in the same class and subclass. This argument is not persuasive because in the biotechnology area there are many more patents per class and subclass than in other arts and because classified patent searches are not the only search performed in examining an application. Applicant asserts that the use of different keywords does not constitute a serious burden. However, conducting a search of multiple protecting groups by keyword or structure does create a different field of search, making the search of the recited protecting groups divergent and not co-extensive.

The requirement is still deemed proper and is therefore made FINAL.

Claims 6, 7, 20-37, 39 and 40 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention or a non-elected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on July 8, 2005.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4, 8, 10, 12, 13, 18 and 38 are rejected under 35 U.S.C. 102(b) as being anticipated by Fung et al. (US 4,757,141).

1. Claim 1 is directed to an oligomeric compound that comprises a plurality of 2'-hydroxyl ribonucleotides and a protected phosphate at the 5' terminus. Claims 2-4 limit claim 1 by stating the terminal phosphate protecting group is intracellularly labile due to intracellular esterases that remove the protecting group to generate a phosphate. Claim 8 limits claim 1 by stating the oligomeric compound is double stranded, while claims 10 and 12 recite that one or both of the two strands comprise a protected phosphate. Claim 13 is directed to the oligomeric compound of claim 1 having the structure shown within the claim. Claim 18 limits claim 13 by defining that R^1 is H and R^2 is a protecting group. Claim 38 is directed to a kit comprising the compound of claim 1. Claims to kits are considered to be a claim to a composition.

2. Fung et al. disclose a phosphoramidite building block suitable to link organic moieties to oligonucleotides. When incorporated into an oligonucleotide, which can be RNA, this building block creates a conjugate shown at column 5, line 25. In this conjugate, W is an oligonucleotide that can be single or double stranded RNA, as stated at line 40-42. When k is 0 there is no R_4 and the conjugate is a diester phosphate. R_1 of Fung et al.'s conjugate is defined at column 3 lines 13-20 as being amino protecting groups such as amides that would be removed intracellularly.

3. Thus, Fung et al. disclose and anticipate claims 1-4, 8, 10, 12, 13, 18 and 38.

Claims 1, 13, 18 and 38 are rejected under 35 U.S.C. 102(b) as being anticipated by Groody (EP 0 266 168).

4. Claims 1, 13, 18 and 38 are described in the previous rejection.

5. Groody discloses a phosphoramidite building block suitable to phosphorylate the 5' terminus of an oligonucleotide and a method of phosphorylating an oligonucleotide. When incorporated into an oligonucleotide, which can be RNA, this building block places a phosphite at the 5' end that after the oxidation step creates a phosphotriester that has the structure shown in claim 13. This structure can be seen in Groody on page 5 on the right side of line 35. Groody discloses that the phosphorus protecting groups (W and X) are chosen from the group of atomic moieties subject to nucleophilic attack or β-elimination and include 2-cyanoethyl, meeting the limitation of claim 18.

6. Thus, Groody discloses and anticipates claims 1, 13, 18 and 38.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-5, 13, 18 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Iyer et al. (WO 96/07392, cited on IDS) in view of Tosquellas et al. (Nucleic Acids Research 1998, vol. 26, pages 2069-2074).

7. Claims 1-4, 13 and 18 are described in the 102 rejection over Fung et al. Claims 5 and 19 limit claims 1 or 13 by stating the phosphorus protecting group (R^2 in claim 13) is S-acetyl-2-thioethyl (SATE).

8. Iyer et al. teach oligonucleotide prodrugs comprising a lipophilic group attached to a 5' phosphate, 3' phosphate or internucleotide phosphate. The lipophilic groups

increase cellular uptake and react with cellular enzymes to generate a natural phosphodiester. Iyer et al. teach at page 19 that the derivatizing group can be any group that is lipophilic and serves to decrease the ionic strength of the oligonucleotide as a whole and at page 21-22 that the derivatized nucleotide is attached at the 5' end, 3' end or at an internucleotide phosphate using any art recognized synthesis protocol. Iyer et al. do not teach the use of SATE as a protecting group.

9. Tosquellas et al. teach the synthesis of pro-oligonucleotides using nucleotide synthons having SATE protecting groups on the internucleotide phosphorus atoms. Tosquellas et al. teach that these pro-oligonucleotides are removed by esterases in cell extracts to provide a natural phosphodiester linkage.

10. It would have been obvious to one of ordinary skill in the art at the time of invention to make oligonucleotide prodrugs containing a lipophilic group at the 5' phosphate position as taught by Iyer et al. using SATE as a protecting group as taught by Tosquellas et al. Iyer et al. provide a motivation to place the lipophilic group at the 5' phosphate, teaching that the oligonucleotide prodrug approach is general and will work at any phosphate position and on any oligonucleotide sequence using synthetic methods known in the art. One of ordinary skill in the art would recognize that the use of a protecting group is mere design choice based on factors such as ease of synthesis and removal and stability of a protecting group under conditions used in subsequent synthesis steps. One of ordinary skill in the art would also recognize that any teaching of a protecting group could be modified using methods routine in the art to place it at any nucleotide position.

11. One of ordinary skill in the art would have had a reasonable expectation of success in placing the SATE protecting group on a 5' phosphate of an oligonucleotide because Tosquellas et al. provide synthons for automated synthesis that can be easily modified by one of ordinary skill in the art to be put at the 5' position of an oligonucleotide.

12. Thus the invention of claims 1-5, 13, 18 and 19 would have been obvious, as a whole, at the time of invention.

Claims 1-4, 8-13, 18 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable Boutla et al. (Current Biology 2001, cited on IDS) in view of Iyer et al. (WO 96/07392, cited on IDS).

13. Claims 1-4, 8, 10, 12, 13, 18 and 38 are described in the 102 rejection over Fung et al. Claims 9 and 11 limit claim 8 by stating the double stranded oligomeric compound comprises one strand that is an antisense strand that optionally contains the protected phosphate group.

14. Boutla et al. teach that siRNAs that are phosphorylated at the 5' end are more active than siRNAs having 5' hydroxyl ends. Boutla et al. do not teach siRNAs having protected phosphate groups.

15. Iyer et al. teach oligonucleotide prodrugs comprising a lipophilic group attached to a 5' phosphate, 3' phosphate or internucleotide phosphate. The lipophilic groups increase cellular uptake and react with cellular enzymes to generate a natural phosphodiester. Iyer et al. additionally teaches at page 3 that it is known in the art to conjugate oligonucleotides with various molecules in order to increase cellular uptake.

16. It would have been obvious to one of ordinary skill in the art to make an siRNA having a 5' phosphorus as taught by Boutla et al. as an oligonucleotide prodrug as taught by Iyer et al. Boutla et al. provide a motivation to make siRNAs with a phosphate at the 5' end by teaching that such siRNAs are more reactive than siRNAs having a 5' hydroxyl group while Iyer et al. provide a motivation to make a phosphorylated oligonucleotide in a lipophilic prodrug form that will be converted to a natural phosphate by a cellular esterase by teaching that oligonucleotide prodrugs containing lipophilic derivatives decrease the ionic strength of an oligonucleotide and increase cellular uptake. One of ordinary skill in the art would have had a reasonable expectation of success in making an siRNA having protected phosphorus at the 5' end because Iyer et al. demonstrate the synthesis of oligonucleotide prodrugs.

17. Thus, the invention of claims 1-4, 8-13, 18 and 38 would have been obvious, as a whole, at the time of invention.

Claims 1-4, 8-18 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Boutla et al. and Iyer et al. as applied to claims 1-4, 8-13, 18 and 38 above, and further in view of Parrish et al. (Molecular Cell 2000, cited on IDS).

18. Claims 1-4, 8-13, 18 and 38 are described in the previous 103 rejection. Claims 14-17 limit claim 13 by stating the oligomeric compound of claim 13 has at least one T_3 position as fluorine (F) optionally with additional T_3 position as a sugar substituent and T_2 as a hydroxyl or a conjugate.

19. The teachings of Boutla et al. and Iyer et al. are described in the previous 103 rejection. Boutla et al. and Iyer et al. do not teach sugar substituents that are fluorine.

20. Parrish et al. teach the functional anatomy of the dsRNA used in RNA interference. Parrish et al. teach that dsRNAs with substitutions routinely used in the art of antisense for providing desirable characteristics such as increased nuclease stability, including 2'-fluoro substitutions, are tolerated in RNA interference.

21. The teachings of Boutla et al. and Iyer et al. are obvious for the reasons given in the previous 103 rejection. It would have been further obvious to make siRNAs having a protected 5' phosphate group and a sugar substituent that is fluorine because Parrish et al. teach that sugar substituents well-known in the art of antisense for providing nuclease stability are tolerated in RNA interference. One of ordinary skill in the art would have had a reasonable expectation of success in making siRNAs having 2'-fluoro substitutions because Parrish et al. teach that double stranded RNAs having this substituent function in RNA interference.

22. Thus, the invention of claims 1-4, 8-18 and 38 would have been obvious, as a whole, at the time of invention.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:45-5:15.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's acting supervisor, Andrew Wang can be reached on 571-272-0811. The central FAX number is 571-273-8300.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Tracy Vivlemore
Examiner
Art Unit 1635

TV
September 13, 2005

J.D. SCHULTZ, Ph.D.
PATENT EXAMINER